I

IAPs
Inhibitor of Apoptosis Proteins: a family of proteins with antiapoptotic effect, probably by inhibiting Caspase-3 and -7. IAP-dependent inhibition of caspase activity is essential for cell survival, and one mechanism for cell death **activation** involves inhibition of IAP function (Wang et al., 1999, Cell, 98: 453-463; Goyal et al., 2000, EMBO, 19: 589-597). For reviews see Deveraux and Reed, 1999, Genes Dev., 13: 239-252 and Miller, 1999, Trends Cell Biol., 9: 323-328. **More**

ICAD
Inhibitor of CAD (Caspase-activated DNase), identified in mouse cells, ICAD is homologous to human DFF45. ICAD binds to **CAD**, and inhibits its DNase activity. Active Caspase-3 cleaves ICAD and by this activates CAD what results in oligonucleosomal DNA cleavage. ICAD is not just inhibitor of CAD but probably also chaperone for CAD, since active CAD is only expressed in presence of ICAD. For a review see Nagata, 2000, Exp. Cell Res. 256: 12-18.

Interferon-gamma
Interferon-gamma; cytokine with antiviral effect produced by cytotoxic CD8+ T lymphocytes and CD4+ Th1 cells but not by Th2 lymphocytes. It inhibits proliferation of T2h cells, activates macrophage functions and regulates antibody production of B lymphocytes.

IGF-BP3
Insulin-like Growth Factor-Binding Protein 3 (IGF-BP3) is a target gene of **p53** and is able to inhibit mitogenic signalling by the insulin-like growth factor IGF-1. IGF-BP3 may link p53 to as yet uncharacterized autocrine/paracrine signalling pathways.

IKAP
IKK-complex-Associated Protein is a scaffold component of the heigh molecular weight IKK complexes. Like NEMO/IKK-gamma, IKAP binds to IKKs directly, but it also binds to NIK. It might direct the assembly or disassembly of IKK complexes in response to signalling, and control deactivation of the kinase complex after stimulation.

IkB proteins
IkB-proteins (**IkB**-**alpha**, beta, and epsilon) are inhibitor proteins of NF-kB, which keep cytosolic NF-kB under tight control by binding to NF-kB and blocking its transport into the nucleus. For NF-kB **activation**, **IkB**-**alpha** is phosphorylated by IKKs at two serine residues what results in the binding of ubiquitin to and degradation of **IkB**-**alpha** by the proteasome.

IKKs
Two **IkB** kinases (IKKs) have been cloned : IKK-**alpha** and -beta. They are the only kinases known to phosphorylate **IkB**-**alpha** at the same residues that are modified in response to agents that activate NF-kB. IKKs are part of multi-protein complexes (800 kDa) which include the IKK-**alpha** and -beta, NEMO/IKK-gamma, IKAP and NIK.

Immune system and Apoptosis
Apoptosis plays an important role in shaping the repertoire of lymphocytes and in regulating the size of the mature lymphocyte pool. In the T cell pool, nonfunctional cells as well as self-reactive cells are eliminated by apoptosis. The best-defined regulators of apoptosis in cells of the immune system are **Fas** and members of the **Bcl-2** family. Fas (CD95) induces apoptosis in activated T cells at the end of an immune response (**AICD**). Fas also functions to maintain T cell tolerance by deleting autoreactive cells and constitutes an important pathway of killing for cytotoxic T cells. The Bcl-2 family proteins, particularly Bcl-2 and Bcl-xL, prevent T cells from undergoing apoptosis in response to various stimuli. Apoptosis

or defects in apoptosis are involved in immunological diseases such as the autoimmune disease **ALPS**, B cell lymphoma, and **AIDS**. **More**

Immunoglobuline fold
The immunoglobulin fold is one of the most versatile and widely-used structural units of proteins. The immunoglobulin fold was originally characterized as the globular modules that form the homology domains of immunoglobulins. Its secondary structure consists of a barrel that is composed of a three- and a four-stranded antiparallel beta-sheet which are linked by a disulfide bond.

INK4 inhibitors
see **Invasiveness**
Invasiveness of tumor cells implies an ability to break loose, enter the blood stream or lymphatic vessels, and form secondary tumors (metastases) at other sites in the body.

HOME of Apoptopedia

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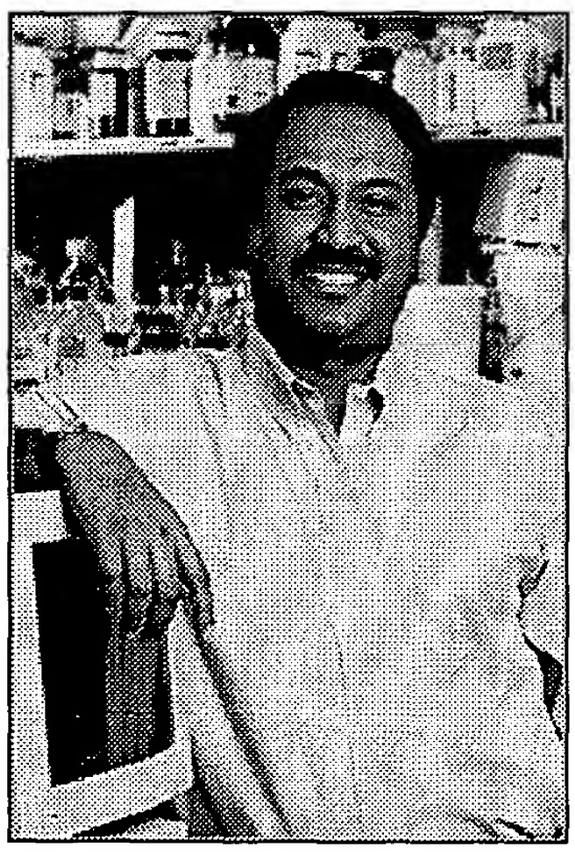
Research Interests



The transcription factor NF-κB plays a critical role in the inducible expression of a large number of genes involved in immune, inflammatory and apoptotic processes. NF-κB can be activated by different stimuli such as microbial products, proinflammatory cytokines, T and B cell mitogens and physical and chemical stresses. NF-κB in turn regulates the inducible expression of many cytokines, chemokines, adhesion molecules, acute phase proteins and anti-microbial peptides. Therefore it appears that NF-kB plays a central, evolutionarily conserved role in coordinating innate immune responses. In unstimulated cells, NF-κB remains inactive in the cytoplasm as an NF-κB:**IκB** complex and treatment of cells with different inducers results in the phosphorylation and subsequent degradation of the **IκB** proteins. Upon degradation of **IκB** the free NF-κB enters the nucleus. The major portion of NF-κB in cells are bound to **IκB-alpha** and **IκB**-beta, two distinct **IκB** isoforms. Research in our laboratory is focused towards understanding both the mechanism by which external signals cause the dissociation of cytosolic NF-κB:**IκB** (**alpha**/beta) complexes, and also the regulation

of NF-κB in the context of innate immune responses and development.

Characterization of kinases involved in NF-κB signalling

Phosphorylation plays a critical role in transducing external signals to NF-κB. The inducible phosphorylation of **IκB-alpha** in response to external signals occurs on two serine residues at the N-terminus of the protein, and is carried out by an **IκB**-kinase complex. The **IκB**-kinase contains two catalytic subunits (IKKalpha and IKKbeta) and a regulatory/adapter protein NEMO (also known as IKKgamma or IKKAP). The mechanism by which various signal transduction pathways interface with the **IκB** kinase complex is not understood and one of our research objectives is to determine the exact role of NEMO in regulating **IκB** kinase activity. We are therefore trying to characterize the interaction domains in NEMO that allow it to respond to different signaling pathways. We are also using biochemical methods to identify and characterize kinases that potentially lie upstream of the **IκB** kinase and might be involved in modulating the catalytic activity of the **IκB** kinase.

Elucidation of components of the Toll/IL-1 signal transduction pathway

TLRs represent a growing family of transmembrane proteins characterized by multiple copies of leucine-rich repeats (LRR) in the extracellular domain and a cytoplasmic Toll/IL-1R (TIR) motif. As their name suggests, TIR motifs of TLRs exhibit significant homology to the intracellular signaling domain of the type I IL-1 receptor (IL-1RI) and therefore, TLRs are thought to belong to the IL-1R superfamily. Although the IL-1R and TLRs differ in their extracellular domains, the presence of the TIR domain allows both receptors to activate similar intracellular signaling pathways. We are therefore interested in characterizing the TLR/IL-1RI induced signal transduction pathways that lead to the **activation** of NF-κB. We have recently identified a novel intermediate in these pathways, named ECSIT, and current efforts are geared towards further characterizing the biological role of ECSIT. It has also been reported recently that signaling from the Toll receptors can lead to apoptosis of immune cells thus leading to a resolution of inflammation following clearance of infection. However the mechanistic explanation for the choice between **activation** or apoptosis through TLR signaling remains unclear, and we are using a variety of biochemical and genetic approaches to examine this issue.

Role of NF-κB in T-lymphocyte development

We have recently demonstrated that **activation** of the transcription factor NF-κB and pre-T cell receptor (pre-TCR) expression is tightly correlated during thymocyte development. Expression of components of the pre-TCR in a T-cell line leads to the constitutive **activation** of NF-κB implying a direct link between the pre-TCR and signaling pathways leading to NF-κB. Inhibition of NF-κB in isolated thymocytes in vitro results in spontaneous apoptosis of cells expressing the pre-TCR, whereas inhibition of NF-κB in transgenic mice through expression of a mutated, super-repressor form of IκBalpha leads to a loss of beta-selected thymocytes. In contrast, the forced **activation** of NF-κB through expression of a dominant active **IκB** kinase allows differentiation to proceed to the CD4+ CD8+ stage in a Rag1-/- mouse that cannot assemble the pre-TCR. Therefore, our results suggested that signals emanating from the pre-TCR are mediated at least in part by NF-κB which provided a selective survival signal for developing thymocytes with productive beta-chain rearrangements. We are currently trying to extend our studies in this area by identifying potential NF-κB target genes in thymocytes. We are also trying to understand whether NF-κB plays a role in the maturation of DP thymocytes to CD4 or CD8 SP thymocytes, since inhibition of NF-κB leads to a selective loss of CD8

SP cells.

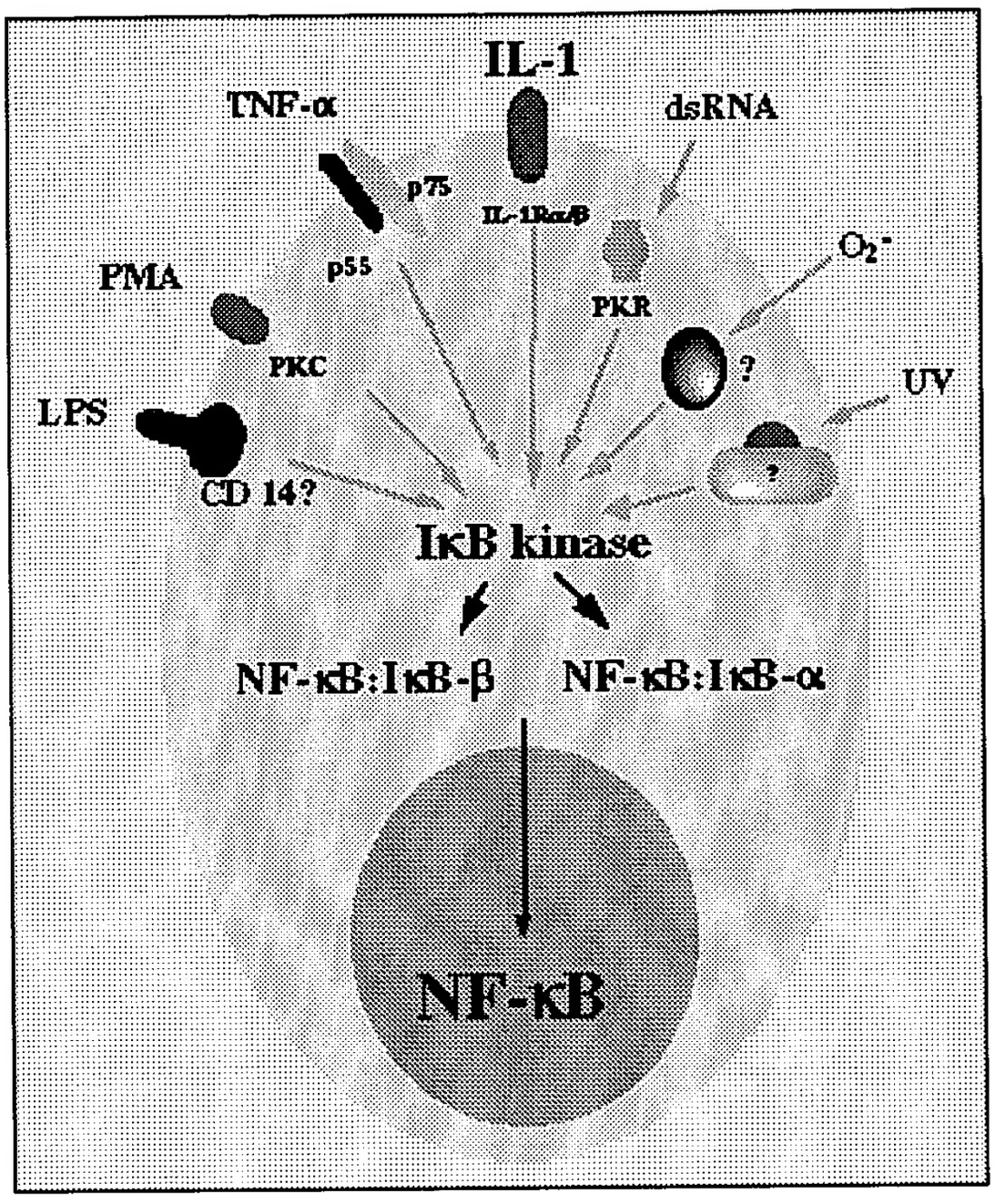


Figure legend: A schematic depiction of the various signal transduction pathways that converge on the **activation** of NF-κB. The details of the signal transduction pathways for all the inducers affecting NF-κB remain to be characterized.

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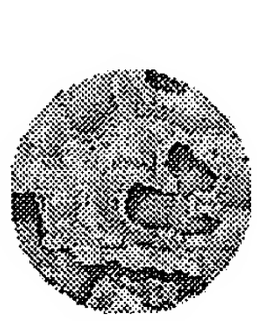


INFLAMMATORY DISEASE

BACKGROUND INFORMATION

March 2000

Cell Adhesion Molecules (CAMs)

Cellular adhesion molecules (CAMs) are a diverse group of glycoprotein and carbohydrate molecules expressed on the surface of virtually every cell in the body in unique patterns according to cell type, state of **activation**, and function. These molecules selectively recognize and bind to one another, mediating the adhesion of cells to cells, and cells to extracellular molecules. They play a critical role in such functions as, 1) organ/tissue development and integrity, 2) migration or trafficking of immune and inflammatory cells to sites of inflammation, 3) initiation and propagation of immune responses, 4) wound healing, and 5) cancer metastasis. CAMs on host cells are also used by viral and bacterial pathogens to selectively gain entrance to specific cells and tissues.

Role of CAMs in Inflammation

Because over-migration of white blood cells into tissues can cause tissue damage and chronic inflammation, drug discovery efforts have focused on the interruption of immune and inflammatory cell trafficking. These processes are mediated by CAMs expressed on immune and inflammatory cells (white blood cells or leukocytes) and the lining cells of blood vessels (endothelial cells). In order to get into tissues where they can inflict immune and inflammatory injury, leukocytes (granulocytes, lymphocytes, and monocytes) must leave the circulation and migrate through the blood vessel wall. This process is mediated by CAMs expressed on the surface of leukocytes which adhere to CAMs expressed on the endothelial cells of blood vessels.

To inhibit the migration of leukocytes from the blood to sites of inflammation in tissues, scientists have specifically targeted CAMs normally expressed at low levels on endothelial cells and greatly up-regulated or over-expressed in disease.

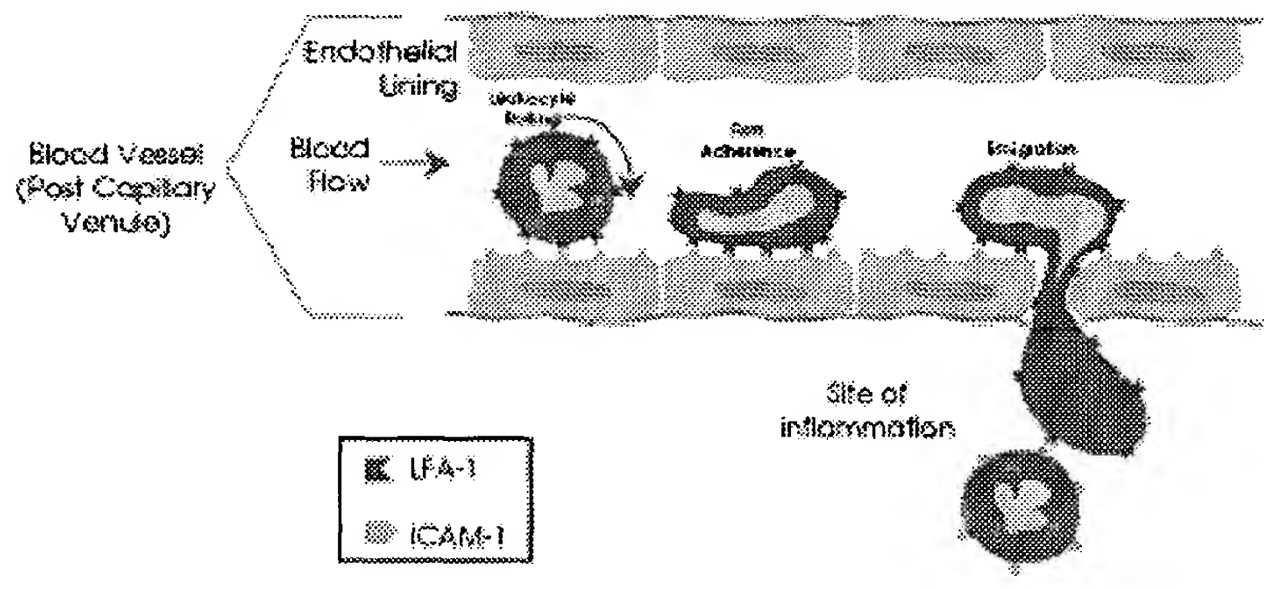
In order to leave the circulation, leukocytes must first stick to the blood vessel surface and then exit between endothelial cell junctions to the tissues. This involves a three-step sequential process

involving rolling of leukocytes along the blood vessel wall, adherence of leukocytes to the blood vessel wall, and finally emigration (transendothelial cell migration). This three-step process is mediated by a series of different endothelial cell-leukocyte CAMs, expressed on the surfaces of both cell types, that recognize and adhere to one another.

There are three basic classes of leukocyte-endothelial cell CAMs, each class comprised of several different molecules that selectively recognize and bind to specific molecules of another class:

- selectins, which recognize carbohydrates;
- integrins, primarily expressed on leukocytes and platelets;
- members of the immunoglobulin superfamily, expressed on both endothelial cells and leukocytes.

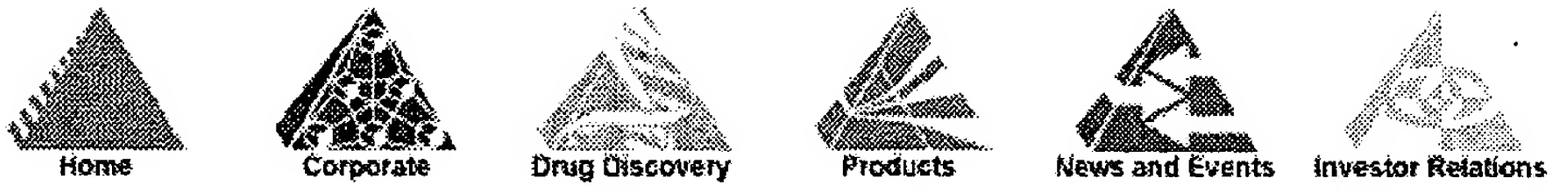
The latter two classes of CAMs primarily recognize and bind to one another. Rolling is mediated by selectins on endothelial cells and leukocytes that recognize carbohydrates on the other cell type. Both adherence and emigration are mediated by integrin-immunoglobulin superfamily binding. The attractiveness of many of these CAMs one for another and/or the number of CAMs expressed on the cell surface may be greatly enhanced during cell **activation** by inflammatory or immune processes.



The Role of ICAM-1 in Inflammatory Disease

The initial focus has been on Intercellular Adhesion Molecule-1 (**ICAM-1**), an inducible member of the immunoglobulin superfamily of CAMs that can be expressed on endothelial cells, antigen presenting cells (cells that allow immune cells to recognize and respond to antigens), and other cell types. **ICAM-1** plays a pivotal role in leukocyte adherence and emigration and important accessory roles in the **activation** of immune and inflammatory cells. It is thought that by blocking or down-regulating **ICAM-1**, it is possible to interfere with the **activation** of immune and inflammatory cells, and the trafficking of these cells to sites of inflammation, thereby suppressing disease expression in a wide variety of inflammatory conditions, such as reperfusion injury that occurs in strokes and heart attacks, rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disease, and organ transplant rejection. **ICAM-1** expression is greatly over-expressed in involved tissues and thereby implicated in the pathogenesis of all of these disease states.

In animal studies, Isis' **ICAM-1** inhibitor has demonstrated significant activity in murine models of cardiac allograft rejection, ulcerative colitis and endotoxin-induced lung inflammation.



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